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(54) Title: HERBAL COMPOSITIONS USEFUL AS CHEMOPREVENTIVE AND THERAPEUTIC AGENTS

(57) Abstract: Compositions derived from traditional Chinese herbal medicines, medicinal plants and extracts thereof, are provided. These compositions can be used as chemopreventive and therapeutic agents.



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## **HERBAL COMPOSITIONS USEFUL AS CHEMOPREVENTIVE AND THERAPEUTIC AGENTS**

5           The present invention relates to compositions comprising herbs and their use  
as chemopreventive and therapeutic agents.

### **BACKGROUND OF THE INVENTION**

10           For the past twenty-five years there has been significant progress in the field  
of cancer research; however, in spite of these positive results, the mortality rate for the  
most common cancers still remains high. Indeed, the goal of the National Cancer  
Institute of a fifty percent reduction in overall cancer mortality by the year 2000 has  
not been met.

15           The term "cancer" is a general one referring to more than 100 forms of the  
disease which may manifest itself in almost every tissue type of the body. Of the  
myriad forms of cancer, lung cancer is the most common cause of death worldwide,  
followed by stomach cancer. Other common forms of cancer include cancers of the  
colon, rectum, breast, prostate, mouth and esophagus.

20

          Lung cancer imposes an enormous burden on health care. The World Health  
Report 2000 estimates that lung cancer has resulted in 860,000 deaths among men and  
333,000 deaths among women per year, and it is the leading cause of cancer deaths  
worldwide. In the United States and Canada, more people are dying from lung cancer  
25       than from breast cancer, colorectal cancer and prostate cancer combined. In addition,  
the incidence of lung cancer in women is rising at an average annual rate of 7% which  
is the most rapid rate of increase for any cancer. The most dominant cause of lung  
cancer is tobacco use, but occupational and environmental exposure to various other  
carcinogenic substances can also influence disease development. In long-term smokers,  
30       the risk of lung cancer never returns to the "baseline" level of a never-smoker, even  
years after smoking cessation. With a large reservoir (100 million in the United States

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and Canada alone) of current and former smokers, who are at risk, lung cancer will continue to be a major health problem for at least several more decades even if current efforts to curb tobacco smoking were successful. The overall five-year survival rate of lung cancer is less than 15%. Despite advances in modern medicine, the survival rate  
5 has not improved substantially over the last two decades. A different approach is therefore needed to control lung cancer.

Prostate cancer is the most commonly diagnosed male malignancy in the United States and the second leading cause of cancer death. It is estimated that in the year  
10 2000, there will be 180,400 new cases and 31,900 deaths caused by prostate cancer. Although prostate cancer responds effectively to orchiectomy or antiandrogen therapy when detected at an early stage, over time, the residual androgen-insensitive cells recolonize, expand, and ultimately establish a hormone-resistant state that often results in fatality. It would be useful, therefore, to have a cancer treatment which could  
15 prevent the proliferation of prostate cancer and maintain it in a dormant state.

The incidence of gastric cancer has fallen in most countries but it is still the most common form of cancer in many countries of East Asia, including China. Globally, gastric cancer is the second most frequent cause of cancer death and it is  
20 estimated that in 1990, there were almost 800,000 new cases and about 630,000 deaths. Similarly, esophageal cancer, the eighth most common cancer worldwide and responsible for 316,000 new cases and 286,000 deaths in 1990, is also very common in China and other Asian countries. Both of these cancers, and especially esophageal cancer, have low survival rates and thus it would be beneficial to have an alternative  
25 treatment approach for these types of cancers.

Traditionally, the focus of cancer research has been in developing therapies and treatments for patients already afflicted with the disease. However, over the last few decades, new insights into the development of cancer as a disease have been gained.  
30 It is now understood that cancer is not the result of a single initiation event but of a gradual, multi-step process characterized by a period of several years between the

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initiation event and the onset of invasive or metastatic disease. In general, the process of carcinogenesis can be divided into three phases: initiation, promotion, and progression. In initiation, a fixed genetic mutation results from the interaction of a carcinogen with DNA. The extent of the molecular change depends on a number of factors including the nature of the carcinogen, the rate and type of carcinogenic metabolism and the response of the DNA repair systems. The next phase, promotion, may occur over extended periods of time and is characterized by the proliferation of the altered cells. This phase may be affected by agents that alter growth rates. During the final phase, progression, genetic and phenotypic changes occur which ultimately cause the development of premalignant lesions into invasive cancer.

The multi-step nature of carcinogenesis suggests the possibility of intervention at a precancerous state. This is the basis for chemoprevention, which refers to the use of natural or synthetic agents to prevent the development of cancer, either by blocking the DNA damage that initiates the carcinogenesis process or by arresting/regressing existing pre-malignant lesions.

Since the mid-1950s, research has been directed at finding compounds with potential chemopreventive properties. The search for these agents has demonstrated a unique challenge. Chemopreventive agents must have low toxicity and be relatively free of side effects because they are intended for administration to healthy people over long periods of time. This is in direct contrast to chemotherapy drugs, such as cis platinum or paclitaxel (Taxol<sup>TM</sup>), which are used as chemotherapeutic agents to treat people already afflicted with cancer. Chemotherapeutic agents are chosen for their ability to kill tumor cells but because they are also toxic to healthy cells, they usually cause harmful side effects.

One of the major sources of potential chemopreventive agents is plants. For example, consumption of cruciferous vegetables, such as broccoli, cauliflower and cabbage is associated with a lower risk of various cancers. Fruits and vegetables contain a number of potentially active chemopreventive compounds, such as

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carotenoids, dithiolthiones and isothiocyanates. They are capable of inhibiting the development of tumors of the lungs, colon, mammary glands and bladder in laboratory animals.

5           Three proof-of-principle clinical trials suggest that chemoprevention might be an effective strategy to control lung cancer. A study by Hong and co-workers in the United States showed that in patients with cured head and neck cancer, high dose 13-cis-retinoic acid for 12 months was more effective than placebo in preventing second primary cancers in the upper aerodigestive tract. However, 13-cis-retinoic acid  
10 at this dosage carries unacceptable toxicity for use in the general population. Another study by Pastorino and co-workers in Europe showed that retinol palmitate in a dose of 300,000 Units per day for 12 months was more effective than placebo in preventing second primary lung cancer. A third study in China found that daily doses of a combination of vitamins and minerals consisting of beta-carotene, vitamin E and  
15 selenium resulted in a 21 % decrease in stomach cancer deaths in high-risk people in China. However, subsequent phase III clinical trials using beta-carotene or retinal (the Alpha-Tocopherol, Beta-Carotene Trial, the Beta-Carotene and Retinol Efficacy Trial, and the EUROSCAN study) failed to show a reduction in lung cancer incidence in high-risk individuals, such as heavy smokers with or without exposure to asbestos,  
20 compared to placebo. In fact, the use of beta-carotene in those who continued to smoke during the study was found to increase the risk of lung cancer. Several reasons were postulated to explain why chemopreventive treatment with retinoids was ineffective or even harmful in active smokers. There may be adverse interactions between tobacco carcinogens and the chemopreventive agent. Beta-carotene, for  
25 example, is a pro-oxidant at high arterial oxygen tension. It can enhance conversion of benzo[A]pyrene to the ultimate carcinogen as well as inducing cytochrome P450. Another reason for the lack of effect in active smokers is that ongoing tobacco carcinogen exposure may counteract the effect of the chemopreventive agent.

30           A number of chemopreventive agents are currently under clinical investigation. Examples of these include fenretinide, selenium, inhaled budesonide, COX-2

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inhibitors, farnesyl transferase inhibitors, lipoxygenase inhibitors, EGF-kinase inhibitors and green tea. Although promising, it remains to be shown if these agents can be shown to be useful in ongoing clinical trials.

5           The best example to-date that chemoprevention can prevent cancer is Tamoxifen. Tamoxifen is an estrogen antagonist. In women at high risk of breast cancer, the Breast Cancer Prevention Trial showed a 49% decrease in invasive cancer and a 50% decrease in non-invasive breast cancer with Tamoxifen versus placebo (J Natl Cancer Inst 1998; 90:1371-88). In addition, there was a decrease in the incidence  
10 of fractures due to osteoporosis. However, there was a slight increase in the risk of endometrial cancer, deep venous thrombosis and pulmonary embolism. More selective estrogen-receptor modulators such as Raloxifene, are being tested against Tamoxifen to determine if these agents may have similar chemopreventive effect but fewer side effects than Tamoxifen.

15           A variety of Chinese herbs have been used for centuries to treat different diseases. The great majority of these are empirical, open, non-randomized studies without placebo control groups. Although some of these herbs have been used to treat patients with cancer, they are not considered to be disease specific. Rather, they are  
20 used for "dispersing heat, detoxification, improving stasis and removing mass". Herbs such as *Sophora tonkinensis*, *Polygonum bistorta*, *Prunella vulgaris*, *Sonchus brachyotus*, *Dictamnus dasycarpus Turcz*, and *Dioscorea bulbifera* are known to have properties that may be useful for the prevention and treatment of cancers. One such composition is known as ZSP or Zeng Sheng Ping; however, the exact formulation of  
25 the composition is not known.

          European Patent application 93 121109.8 describes a composition comprising *Sophora tonkinensis* Gapnep 42 mg, *Polygonum bistorta* L. 42 mg, *Prunella vulgaris* L. 42 mg, *Sonchus brachyotus* DC 42 mg, *Dictamnus dasycarpus Turcz* 21 mg, and  
30 *Dioscorea bulbifera* 10 mg which was reported to be useful for the treatment of patients with mouth, esophagus or digestive tract cancers. Thus, there is a need to

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develop other herbal remedies for the treatment and prophylaxis of common cancers, and for other therapeutic uses.

## 5 SUMMARY OF THE INVENTION

Thus, according to the present invention there is provided a composition comprising herbs.

Thus, according to this embodiment of the invention, there is provided a  
10 composition comprising a mixture of at least three different herbs selected from the group consisting of herbs, which for the purpose of this invention have been designated as: Herb A, Herb B, Herb C, Herb D, Herb E and Herb F.

In the composition defined in EPO 93121109.8 the herb corresponding to Herb  
15 A was *Sophora tonkinensis* (*Sophora subprostrata*). According to the present invention it has been found that any one of the following herbs can be used in place of *Sophora tonkinensis*:

*Belamcanda chinensis*  
*Scrophularia ningpoensis*.  
20 *Isatis tinctoria*  
*Isatis indigotica* or  
*Baphicacanthus cusia* Bremek.

In the composition defined in EPO 93121109.8 the herb corresponding to Herb  
25 B was *Polygonum bistorta*. According to the present invention it has been found that any one of the following herbs can be used in place of *Polygonum bistorta*:

*Polygonum lapidosum*  
*Polygonum viviparum*  
*Polygonum manshuriense*  
30 *Polygonum alopecuroides*  
*Polygonum sphaerostachyum*

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*Andrographis paniculata*  
*Taraxacum mongolicum* or  
*Chrysanthemum indicum*.

- 5           In the composition defined in EPO 93121109.8 the herb corresponding to Herb C was *Prunella vulgaris*. According to the present invention it has been found that any one of the following herbs can be used in place of *Prunella vulgaris*:

*Artemisia capillaris*  
*Gardenia jasminoides*  
10           *Rosa rugosa* or  
*Lophatherum gracile*.

- In the composition defined in EPO 93121109.8 the herb corresponding to Herb D was *Sonchus brachyotus*. According to the present invention it has been found that  
15           any one of the following herbs can be used in place of *Sonchus brachyotus*:

*Patrinia scabiosaefolia*  
*Patrinia villosa*  
*Sonchus arvensis*  
*Thlaspi arvense*  
20           *Portulaca oleracea* or  
*Pulsatilla chinensis*.

- In the composition defined in EPO 93121109.8 the herb corresponding to Herb E was *Dictamnus dasycarpus*. According to the present invention it has been found  
25           that any one of the following herbs can be used in place of *Dictamnus dasycarpus*:

*Kochia scoparia*  
*Sophora flavescens* or  
*Heydyotis diffusa*.



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In the composition defined in EPO 93121109.8 the herb corresponding to Herb F was *Dioscorea bulbifera*. According to the present invention it has been found that any one of the following herbs can be used in place of *Dioscorea bulbifera*:

- Panax notoginseng*
- 5 *Bletilla striata*
- Nelumbo nucifera*
- Polygonum bistorta*
- Cephalanoplos segetum*
- Cirsium japonicum*
- 10 *Sophora japonica*
- Typha angustifolia*. or
- Rubia cordifolia*.

Further according to the present invention there is provided a use of said  
15 composition as chemopreventive and therapeutic agents.

#### DETAILED DESCRIPTION OF PREFERRED EMBODIMENT

The present invention relates to compositions comprising herbs and their use  
as chemopreventive and therapeutic agents.

20

In one embodiment of the present invention the composition comprises a mixture of at least three different herbs, known hereinafter as Herb A, Herb B, Herb C, Herb D, Herb E and Herb F.

25 According to the present invention Herb A is selected from the group consisting of:

- Belamcanda chinensis*
- Scrophularia ningpoensis*
- Isatis tinctoria*
- Isatis indigotica* and
- 30 *Baphicacanthus cusia*.

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- According to the present invention Herb B is selected from the group consisting  
of: *Polygonum lapidosum*  
*Polygonum viviparum*  
*Polygonum manshuriense*  
5 *Polygonum alopecuroides*  
*Polygonum sphaerostachyum.*  
*Andrographis paniculata*  
*Taraxacum mongolicum* and  
*Chrysanthemum indicum.*  
10
- According to the present invention Herb C is selected from the group consisting  
of: *Artemissia capillaris*  
*Gardenia jasminoides*  
*Rosa rugosa* and  
15 *Lophatherum gracile.*
- According to the present invention Herb D is selected from the group consisting  
of: *Patrinia scabiosaefolia*  
*Patrinia villosa*  
20 *Sonchus arvensis*  
*Thlaspi arvense*  
*Portulaca oleracea* and  
*Pulsatilla chinensis.*
- 25 According to the present invention Herb E is selected from the group consisting  
of: *Kochia scoparia*  
*Sophora flavescens* and  
*Heydyotis diffusa.*
- 30 According to the present invention Herb F is selected from the group consisting  
of : *Panax notoginseng.*

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*Bletilla striata*

*Nelumbo nucifera.*

*Polygonum bistorta*

*Cephalanoplos segetum .*

5       *Cirsium japonicum.*

*Sophora japonica*

*Typha angustifolia* and

*Rubia cordifolia.*

10           When, according to the present invention, the composition comprises three different herbs, one of which is selected from each of Herb A, Herb B, Herb C, Herb D or Herb E, each of the three herbs are present in an amount from about 9 % to about 57 %. In a further example of this embodiment, the three herbs are each present in an amount from about 15 % to about 50 %. In a further example of this embodiment, each  
15       of the three herbs are present in an amount from about 25 % to about 40 %. In a further example of this embodiment, each of the three herbs are present in an amount of about 33 %.

              When the composition comprises four different herbs, one of which is selected  
20       from each of Herb A, Herb B, Herb C, Herb D or Herb E, each of the four herbs are present in an amount from about 6 % to about 43 %. In a further example of this embodiment, each of the four herbs are present in an amount from about 15 % to about 35 %. In a further example of this embodiment, each of the four herbs are present in an amount of about 25 %.

25           In a further example of the present invention, when the composition comprises four herbs, three of which are selected from the group consisting of Herb A, Herb B, Herb C, Herb D and the fourth herb is selected from the group consisting of Herb E. The composition of the first three herbs are each present in an amount from about 7 %  
30       to about 57 % and the fourth herb is present in an amount from about 3.5 % to about 28.5 %. In a further example of this embodiment, each of the first three herbs are

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present in an amount from about 15% to about 48% and the fourth herb is present in an amount from about 7.5% to about 24%. In a further example of this embodiment, the first three herbs are present in a composition in an amount of about 20% to about 43%, and the fourth herb is present in an amount from about 10% to about 21.5%.

5 In a further example of this embodiment, the first three herbs are present in an amount of about 28% and the fourth herb is present in an amount of about 14%.

In yet a further embodiment of this invention, the composition comprises five different herbs, one of which is each selected from Herb A, Herb B, Herb C, Herb D

10 or Herb E, each of the five herbs are present in an amount from about 5% to about 35%. In a further example of this embodiment, each of the five herbs are present in an amount from about 10% to about 30%. In yet a further example of this embodiment, each of the five herbs are present in an amount from about 15% to about 25%. In a further example of this embodiment, each of the five herbs are present in

15 an amount of about 20%.

In yet a further embodiment of this invention, the first four herbs are selected one from each of the group Herb A, Herb B, Herb C and Herb D whereas the fifth herb is selected from Herb E and the first four herbs are present in an amount from

20 about 6% to about 38%, whereas the fifth herb is present at an amount from about 3% to about 19%. In a further example of this embodiment, the first four herbs are present in the composition at an amount from about 12% to about 32%, and the fifth herb is present in an amount from about 6% to about 16%. In yet a further example of this embodiment, the first four herbs are present in an amount from about 18% to

25 about 26% and the fifth herb is present in an amount from about 9% to about 13%. In yet a further example of this embodiment, the first four herbs are present at an amount of about 22%, whereas the fifth herb is present at an amount of about 11%.

In yet a further embodiment, the composition comprises six herbs. The first

30 five herbs are selected from the group consisting of Herb A, Herb B, Herb C, Herb D and Herb E, and the sixth herb is selected from Herb F and the first five herbs are

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present in an amount from about 5% to about 31% and the sixth herb is present in an amount from about 2.5% to about 17.5%. In a further example of this embodiment, each of the first five herbs are present in an amount from about 10% to about 26%, and the sixth herb is present in an amount from about 5% to about 15%. In a further  
5 example of this embodiment, the first five herbs are each present in an amount from about 15% to about 21% and the sixth herb is present in an amount from about 7.5 to about 12.5%. In a further example of this embodiment, the first five herbs are present in an amount from about 18% and the sixth herb is present in an amount from about 10%.

10

In yet a further example of this embodiment, the first four herbs are selected from the group of Herb A, Herb B, Herb C or Herb D. The fifth herb is selected from Herb E and the sixth herb is selected from Herb F, wherein the first three herbs are each present in an amount from about 5% to about 38%, the fifth herb is present in an  
15 amount from about 2.5% to about 19% and the sixth herb is present in an amount from about 1.75% to about 9.5%. In a further example of this embodiment, the first four herbs are present in an amount from about 10% to about 33%. The fifth herb is present in an amount from about 5% to about 16.5% and the sixth herb is present in an amount from about 3% to about 8.25%. In yet a further example of this  
20 embodiment, the first four herbs are present in an amount from about 15% to about 28%; herb five is present in an amount from about 7.5% to about 14.5% and the sixth herb is present in an amount from about 4.25% to about 7%. In yet a further example of this embodiment, the first four herbs are present in an amount from about 21%. The fifth herb is present in an amount from about 10.5% and the sixth herb is present  
25 in the amount from about 5.5%.

It is important to ensure that the herbs which are used according to the present invention are selected such that they contain only acceptable levels of contaminants such as metals or pesticides. Various regions of China have been surveyed and it was  
30 found that the component herbs can be harvested from the Guangxi, Hunan, Liaoning, Anhui, Hebei and Jiangsu regions of China during the summer and autumn months and

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no pesticides are used. The plants are purchased dried and whole or parts of these herbs are used in manufacturing.

5 The general manufacturing scheme is as follows: the herbs are either subjected to an aqueous extraction, the aqueous extract is then filtered if necessary to remove large particles, the aqueous extract is then dried to a powder. Alternatively, it is possible to use the herbs directly by grinding to a powder. The powdered herbs are then used in the production of the therapeutic in a variety of forms for administration.

10 Any suitable mode of delivery can be used according to the present invention. For example the composition of the present invention can be delivered orally by a pill, tablet, drink, candy or paste. The composition can also be delivered as a transdermal patch, by inhalation or suppository. Delivery of the composition as an injectable is also possible, according to the present invention. Therefore, the composition can be  
15 administered as a therapeutic agent or as a dietary supplement.

In one embodiment of the present invention, tablets are formulated into 0.3g tablets. A typical daily dosage is about 1.2 to 6 g/day based on the body weight and/or severity of the condition.

20

According to the present invention the compositions are useful for a variety of therapeutic treatments. In one embodiment of the present invention the compositions are useful for the prevention or treatment of cancers.

25 According to one embodiment of the present invention, the composition comprises additional therapeutic agents. Examples of such agents can include, but are not limited to, chemotherapeutic agents.

30 As will be apparent to those skilled in the art in light of the foregoing disclosure, may alterations and modifications are possible in the practice of this invention without departing from the spirit or scope thereof. Accordingly, the scope

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of the invention is to be construed in accordance with the substance defined by the following claims.

**Claims:**

1. A composition comprising a mixture of at least three different herbs  
selected from the group consisting of: Herb A, Herb B, Herb C, Herb D,  
5 Herb E and Herb F; wherein  
Herb A is selected from the group consisting of:  
*Belamcanda chinensis*  
*Scrophularia ningpoensis*  
*Isatis tinctoria*  
10 *Isatis indigotica* and  
*Baphicacanthus cusia*;  
Herb B is selected from the group consisting of:  
*Polygonum lapidosum*  
*Polygonum viviparum*  
15 *Polygonum manshuriense*  
*Polygonum alopecuroides*  
*Polygonum sphaerostachyum*  
*Andrographis paniculata*  
*Taraxacum mongolicum* and  
20 *Chrysanthemum indicum*;  
Herb C is selected from the group consisting of:  
*Artemisia capillaris*.  
*Gardenia jasminoides*  
*Rosa rugosa* and  
25 *Lophatherum gracile*;  
Herb D is selected from the group consisting of:  
*Patrinia scabiosaefolia*.  
*Patrinia villosa*  
*Sonchus arvensis*  
30 *Portulaca oleracea* and  
*Pulsatilla chinensis*;



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Herb E is selected from the group consisting of:

*Kochia scoparia*

*Sophora flavescens* and

*Heydyotis diffusa*; and

5 Herb F is selected from the group consisting of:

*Panax notoginseng*

*Bletilla striata*

*Nelumbo nucifera*

*Polygonum bistorta*

10 *Cephalanoplos segetum*

*Cirsium japonicum*

*Sophora japonica*

*Typha angustifolia* and

*Rubia cordifolia*.

15

2. The composition of Claim 1 wherein, the composition comprises three herbs, one of which is selected from each of Herb A, Herb B, Herb C, Herb D or Herb E and wherein each is present in an amount from about 9% to about 57%.

20

3. The composition of Claim 1, wherein the composition comprises four herbs, one of which is selected from each of Herb A, Herb B, Herb C, Herb D or Herb E, and wherein each is present in an amount from about 6% to about 43%.

25

4. The composition of Claim 1, wherein the composition comprises four herbs, the first three are selected from the group consisting of Herb A, Herb B, Herb C and Herb D and are present in an amount from about 7% to about 57% and the fourth is selected from Herb E and is present in an amount
- 30 from about 3.5% to about 28.5%.

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5. The composition of Claim 1, wherein the composition comprises five herbs, one of which is selected from each of Herb A, Herb B, Herb C, Herb D or Herb E, and wherein each is present in an amount from about 5% to about 35%.
- 5
6. The composition of Claim 1, wherein the composition comprises five herbs, and wherein the first four herbs are selected from the group consisting of Herb A, Herb B, Herb C and Herb D and are present in an amount from about 6% to about 38% and the fifth herb is selected from Herb E and is present in an amount from about 3% to about 19%.
- 10
7. The composition of Claim 1, wherein the composition comprises six herbs, and wherein the first five herbs are selected from the group consisting of Herb A, Herb B, Herb C, Herb D and Herb E wherein the herbs are present in an amount from about 5% to about 31% and the sixth herb is selected from Herb F and is present in an amount from about 2.5% to about 17.5%.
- 15
8. The composition of Claim 1, wherein the composition comprises six herbs, and wherein the first four herbs are selected from the group consisting of Herb A, Herb B, Herb C or Herb D and are present in an amount from about 5% to about 38% and the fifth is selected from Herb E and is present in an amount from about 2.5% to about 19% and the sixth herb is selected from Herb F and is present in an amount from about 1.75% to about 9.5%.
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## INTERNATIONAL SEARCH REPORT

Int ional Application No

PCT/CA 02/00204

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 A61K35/78

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                       | Relevant to claim No. |
|------------|--|-----------------------|
| X          | EP 0 665 017 A (HENNE KURT)<br>2 August 1995 (1995-08-02)<br>claim 1<br>---  | 1-8                   |
| X          | EP 0 568 001 A (NAMBA TSUNEO ;SHIRAKI<br>KIMIYASU (JP))<br>3 November 1993 (1993-11-03)<br>claim 1<br>---                | 1                     |
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

28 May 2002

Date of mailing of the international search report

06/06/2002

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

Int. Patent Application No  
PCT/CA 02/00204

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |   |                       |
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| X  | US 4 459 285 A (GROLLIER JEAN F ET AL)<br>10 July 1984 (1984-07-10)<br>claim 1<br>column 2, line 28,39,60<br>column 3, line 17,22,34<br>----- | 1-8                   |

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 02/00204

| Patent document<br>cited in search report |   | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
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